REMARKS

Claims 27, 29, 31-37, 39, 43-46 and 48 were pending in the present application. Claims 1-19 and 22-26 had been previously withdrawn from the present application and have now been canceled. Accordingly, claims 27, 29, 31-37, 39, 43-46 and 48 will be pending upon entry of the instant amendment. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite prosecution of the application. No new matter has been added, and Applicants submit that all of the claims are now in condition for allowance.

Objections to the Disclosure

The Examiner objected to the disclosure because the specification contained hyperlinks and/or other forms of browser-executable code.

The specification has been amended to address the objections of the Examiner. It is believed the amendments contained herein render the present objections moot. Reconsideration and withdrawal of the objections is respectfully requested.

The Rejection of Claims 27, 29, 31-37, 39, 43-46 and 48 under 35 U.S.C. §101,Should Be Withdrawn

Claims 27, 29, 31-37, 39, 43-46 and 48 were rejected under 35 U.S.C §101 because the claimed invention purportedly is not supported by a credible, substantial, specific, or well-established utility. This rejection is respectfully traversed.

The standards for establishing utility sufficient to meet the requirements of 35 U.S.C. §101 are laid out in the "Utility Examination Guidelines" published in the January 5, 2001 Federal Register (hereinafter "Utility Guidelines"). 66 Fed. Reg. 1092 (2001). Specifically, the guidelines set forth two situations for satisfying the utility requirement: where Applicant has a well established utility, as it would be clear from reading the specification and claims that the invention has a well established utility, and where Applicant has asserted a specific and substantial utility that is credible. In order to make an effective rebuttal of utility, the Examiner must make a prima facie showing that either there is no well established utility or that Applicants' asserted utility is either not specific, substantial, or credible. Applicants respectfully submit that Applicants specification as filed has a well established utility. Still further, Applicants submit an asserted specific substantial and credible utility has been set forth in the

application as filed. For the reasons discussed below, reconsideration of the rejection is requested.

I. The application as filed has a well established utility.

According to the Utility Examination Guidelines:

If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. See MPEP §2107 II (A) (3). Contrary to the Examiner's assertions, as demonstrated below, the VR2 proteins of the present invention have a well established, credible and substantial utility. Applicants respectfully submit one of skill in the art would immediately appreciate why the invention disclosed and claimed in the present application was useful based on the characteristics of the disclosed human vanilloid receptor (hVR2).

The importance of vanilloid receptors as potential mediators of nociception had been well established prior to the cloning of the first mammalian vanilloid receptor. Artisans of skill in the art had already determined that vanilloids bound to a receptor which was expressed in cells of the central nervous system (e.g. in sensory neurons) and that these receptors could be used therapeutically to alleviate neuropathic pain (Szallasi A. *et al.* Pain. 1996 Dec; 68(2-3): 195-208). The rat VR1 cDNA was cloned in 1997, it was shown to be structurally similar to TRP family members and it was shown to be activated by increases in temperature in the noxious range (Caterina M.J. *et al.* Nature. 1997 Oct 23; 389(6653): 816-24). The specification as filed sets forth the identification of a human paralogue of rat VR1, as identified through sequence homology, as acknowledged by the Examiner. Thus, Applicants submit one of skill in the art would immediately appreciate the utility of the newly identified family member of the vanilloid receptor as being useful in identification of modulators of pain.

II. Applicants have asserted a specific, substantial and credible utility.

At the time of filing of the present application, the inventors recognized that they had cloned a human vanilloid receptor (hVR-2) due to its structural similarities to the rat VR1. The inventors also recognized that this polypeptide represented a unique target for pain and that it

was useful in the identification of modulators of chronic neuropathic pain. Such recognition and asserted utility is set forth throughout the specification. See, *e.g.*, page 3, lines 1-6. Applicants submit the utility asserted in the specification as filed is sufficient to support a credible, substantial, and specific utility to meet the requisite standard for utility under the present guidelines of the USPTO that the presently claimed compositions are useful in the identification of compounds which bind to the hVR-2 polypeptide. Applicants have provided the composition comprising the nucleic acid and proteins comprising hVR-2, a new member of the vanilloid family of receptors, as well as description of assays to determine activity of hVR2, including, for example, heat activation. Such assays are set forth as useful for identification of pain modulators. As described below, work performed by numerous other groups since the time of filing of the present invention, have further substantiated the asserted utility of the cloned hVR-2 of the present invention.

a. TRPV family members

At present, the TRPV family of proteins consists of six members, namely 1) TRPV1 (also known as vanilloid receptor 1, VR1 or capsaicin receptor); 2) TRPV2 (also known as vanilloid receptor like-1, VRL1 and in the present application VR2); 3) TRPV3 (also known as vanilloid receptor-related osmotically activated channel, VROAC, OSM9-like transient receptor potential channel 4, TRPC4 and TRP12); 4) TRPV4 (also known as vanilloid receptor-like protein 3 or VRL3); 5) TRPV5 (also known as epithelial calcium channel 1, ECAC1, CaT2, ECaC and OTRPC3); and 6) TRPV6 (also known as epithelial calcium channel 2, ECAC2, CaT, CaT1 and CaT-like).

b. Sequence similarity between members of the TRPV family of proteins

As mentioned, there are now six member of the TRPV family of proteins. These paralogues were identified by performing bioinformatics analyses, structural analyses and by performing experiments to further characterize members. At the amino acid level, the sequence identities of the members identified to date are all within a very narrow range of percentages. The percent identities between TRPV1, TRPV2, TRPV3 and TRPV4 are all between 41% and 47%, whereas between the calcium selective TRPVs (TRPV5 and 6) and the nonselective cation TRPVs (TRPV1-4), the percent identities are all between 30% to 33%. The percent identity between the two calcium specific TRPVs (TRPV5 and 6) is somewhat higher at 75% (refer to Fig II of Gunthorpe M.J., et *al.*, TRENDS in Pharma. Sciences 2002; 23(4) 183:191). TRPV1, TRPV2, TRPV3 and TRPV4 are also structurally very similar, each consisting of a cytoplasmic

N-terminus domain containing 3 ankyrin-repeat domains, 6 transmembrane domains, a putative pore-loop region and a C-terminal cytoplasmic tail. Due to this sequence and structural similarity, artisans of skill in the art have established that these molecules all do in fact belong to the same family.

c. Functional similarity between members of the TRPV family of proteins

TRPV1-TRPV4 family members of this growing family are well characterized as temperature-gated channels, each having different temperature thresholds (Benham C.D. et *al.*, Cell Calcium 2003; 33(5-6):479-487). TRPV5 and TRPV6 family members, unlike the TRPV1-TRPV4 family members which are nonselective cation channels, are highly selective for calcium and are constitutively active.

III. The Examiner has not made an effective *prima facie* showing of lack of utility

In order to rebut an asserted utility, an Examiner must: *make a prima facie showing of no specific and substantial credible utility and the Examiner must establish* ***that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted*** *by the applicant for the claimed invention.* See MPEP §2107 II (C) (2). Applicants submit the Examiner has not met the requisite requirement to rebut Applicants asserted utility.

Firstly, the Examiner states on page 3 of the Office Action that there is 41.3% identity between the amino acid sequence of hVR-2 and the known rat capsaicin VR-1, and as such "[o]ne of skill would not conclude that these two different proteins bind the same ligand or spectrum of ligands. Further, given that VR-1 and VR-2 exhibit substantially different patterns of expression as described on page 63 of the instant specification, one would not conclude that VR-2 mediates nociception simply because of its limited structural similarity." Applicants respectfully traverse this rejection, and posit that the effects of sequence dissimilarities upon protein structure and function can indeed be predicted in some cases. Furthermore, as discussed above, all members of the TRPV family of proteins have a narrow range of sequence similarities, that the nonselective cation members are structurally very similar and that it is well accepted by artisans of skill in the art that these proteins belong to the same family. Still further, the fact that the VR-1 and VR-2 proteins exhibit different patterns of expression does not necessarily lead one to conclude that the VR-2 protein does not mediate nociception. One could envision that the two family members could mediate nociception in different cell types. In fact, as described by

Stenholm E. *et al.* (Acta. Odontol. Scand. 2002 Mar;60(2):72-79), VR1 and VRL-1 (hVR-2) rarely co-exist in the same cells, but rather are confined to separate subpopulations.

Secondly, the Examiner states that "The disclosure in the instant specification that the hVR-2 protein described therein is structurally related to capsaicin receptor VR-1 does not support a conclusion that hVR-2 will bind vanilloids and/or capsaicin." and that "[o]ne of ordinary skill would not believe that hVR-2 is a capsaicin receptor or that it mediates nociception." Applicants respectfully disagree and point the Examiner to Example 4 at page 70 of the specification. As described therein, hVR-2 was subcloned into an oocyte expression vector and then subsequently injected into oocytes for further characterization. These studies demonstrate that the hVR-2 can in fact be activated by heat stimulation. Additionally, the vanilloid receptor antagonist capsazepine was shown to reversibly block the heat response of VR2. Applicants have therefore shown that 1) hVR-2 is sensitive to heat stimulation and 2) hVR-2's heat sensitivity can be reversibly blocked by a vanilloid receptor antagonist, namely capsazepine. Sensitivity to heat is a critical aspect of nociception. In fact, hVR-2 has been later shown to have a higher temperature threshold than VR1 (Caterina, M.J. et al., Nature 1999; 398, 436-441). The fact that the hVR-2 protein is a heat-sensitive cation channel that is involved in nociception has been further substantiated by many other groups.

Thirdly, the Examiner characterizes the hVR-2 protein as an "orphan protein" and states that "In the absence of knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it." The Examiner further asserts that the instant situation is analogous to that addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966). Applicants respectfully disagree. This situation is not analogous to *Brenner v. Manson* for the following reasons. In the instant application, Applicants have identified hVR-1 and hVR-2 and have characterized these proteins as vanilloid receptors due to their close identity and structural similarity to the rat VR1 sequence. Applicants further performed experiments demonstrating, in the case of hVR-2, that it confers sensitivity to temperature (and can be inhibited by a known vanilloid receptor inhibitor) and is therefore involved in nociception (Example 4 within the specification), thus validating the asserted utility.

The Examiner states on page 5 of the Office Action, that "There is absolutely no evidence of record or any line of reasoning that would support a conclusion that a protein of the instant invention is associated with the plurality of disorders that are listed in lines 11-20 on page 9 of the instant specification." Applicants assert that a showing of specific diseases which are in fact

demonstrated to be treatable by the invention is not necessary. The Examiner focuses on the specific biological significance and seemingly the required efficacious use of identified compounds as Applicants requirement to satisfy the utility requirement. Applicants respectfully submit this focus is undue and improper. Still further, the utility of identification of targets for screening for therapeutics in the pharmaceutical industry is a well established recognized utility for receptors useful in biological responses such as those identified and asserted in the present application as useful in identification of modulators of pain.

Additionally, Applicants submit that the Examiner has not made a sufficient showing to establish, more likely than not, the utility set forth in the present specification would not be specific or substantial, as sufficient support or factual findings have not been relied upon to make such a showing to rebut Applicants' assertion that the use in identification of therapeutics would more likely than not be useful. The Examiner makes a generic statement as to disbelief of the asserted utility because the molecule has not been de-orphaned. However, this is not sufficient to meet the requisite standard that, it is more likely than not, that one of skill in the art would doubt Applicants' asserted utility. In fact, as described herein, Applicants assertion was correct and has been supported by later validation work of Applicants and others. Applicants submit the Examiner has not made a sufficient showing to establish, more likely than not, the utility set forth in the present specification would not be specific or substantial, as sufficient support or factual findings have not been relied upon to make such a showing to rebut Applicants' assertion that the use in identification of therapeutics would more likely than not be useful. Rather, the Examiner relies on general arguments to back up his claim that Applicants' original assertion is incorrect. As such, Applicants submit maintenance of the present rejection is improper.

Thus, Applicants submit that the application as filed sets forth the hVR-2 proteins of the invention which have a well established, credible and substantial utility. Still further, Applicants submit a specific, substantial and credible utility has been set forth, as described in further detail above. The Examiner has not provided the preponderance of evidence required by the Utility Guidelines to establish the utility asserted for the hVR-2 proteins of the invention is, in view of the whole record, more likely than not neither credible, specific, or substantial. Therefore, Applicants respectfully request reconsideration and withdrawal of the foregoing 35 U.S.C. § 101 rejection over claims 27, 29, 31-37, 39, 43-46 and 48.

Rejection of Claims 27, 29, 31-37, 39, 43-46 and 48 under 35 U.S.C. §112, first paragraph

Claims 27, 29, 31-37, 39, 43-46 and 48 were rejected under 35 U.S.C §112, first paragraph, as "[f]ailing to adequately teach how to use the instant invention", based on the rejection of these claims under 35 U.S.C §101.

For the reasons discussed above, Applicants have in fact established utility for the hVR-2 proteins of the invention, as well as the screening assays to identify compounds which bind to the hVR-2 proteins. Applicants therefore request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejection over claims 27, 29, 31-37, 39, 43-46 and 48.

Rejection of Claims 43-46 and 48 under 35 U.S.C. §112, first paragraph

Claims 43-46 and 48 were rejected under 35 U.S.C §112, first paragraph, because "[t]he specification, while providing the guidance needed to practice a method of identifying a ligand which binds to a receptor protein comprising the amino acid sequence presented in SEQ ID NO:5 of the instant specification, does not reasonably provide the guidance needed to practice a binding assay which employs a protein having anything less than the entire amino acid sequence presented in SEQ ID NO:5".

Specifically, the Examiner states that "[i]n the absence of both working examples of intentionally altered VR-2 proteins and information on the ligand and signaling pathway of the disclosed protein an artisan could not alter a single amino acid residue in SEQ ID NO:5 with any confidence that the resulting protein will function in a manner that is representative of its native analog and the instant specification does not disclose how to use information that is obtained from an assay which employs a protein that does not function in a manner that is representative of its native analog." Applicants respectfully traverse this rejection for the reasons stated below.

Independent claims 46 and 48 of the instant application are directed to methods of identifying a compound which bind to a polypeptide that is at least 95% identical to the amino acid sequence of SEQ ID NO:5 and which is capable of modulating membrane excitability in a cell. Contrary to the Examiner's assertion, Applicants have provided teachings for every element needed for one of skill in the art to practice the claimed invention. First, Applicants have taught the domains within the VR-2 polypeptide which are conserved among vanilloid receptors and which are essential for activity of the polypeptide (*e.g.* an ankyrin-repeat domain, 6 transmembrane domains and a proline rich domain) (see page 10 of specification). Second, by having identified the regions necessary for activity, one of skill in the art would understand

which regions of the polypeptide are amenable to alterations as well as those which are not amenable to alterations (those necessary for activity). Third, the specification teaches one how to generate functional variants by performing conservative substitutions within the polypeptide used in the claimed invention (see *e.g.* at page 17, "[c]onservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain."). Applicants have also given examples known in the art about which of the amino acids have similar side chains (see page 18 of specification), thereby providing a skilled artisan the necessary tools to generate functional variants of the polypeptide used in the claimed invention.

Finally, presently pending claims 46 and 48 stipulate that the polypeptide which is 95% identical to SEQ ID NO:5 must also be capable of modulating membrane excitability in a cell. As indicated in Applicants' earlier reply, the methods described in the present specification and the methods which were well known by artisans at the time of filing, both allow one of skill in the art to readily test whether a polypeptide is capable of modulating membrane excitability in a cell. Applicants have additionally provided a specific assay which could be easily used to test whether candidate mutated polypeptides retain the native protein's function in a manner that is representative of its native analog. Such an assay would involve, for example, performing an assay using oocyte expression vectors which is described in Example 4 of the specification. Performing such an assay to determine whether or not a candidate mutant polypeptide of SEQ ID NO:5 has the desired properties is clearly taught and readily available to one of skill in the art. Still further, preparation of constructs and performance of such assays would not constitute undue experimentation. Therefore, Applicants have provided all of the necessary information to enable one of skill in the art to 1) identify regions within the polypeptide used in the claimed invention which may be altered while maintaining activity; 2) generate mutants within the 95% criteria; and 3) perform assays to determine whether or not the candidate mutated polypeptides generated do in fact have the desired VR-2 activity.

Therefore, contrary to the Examiner's assertions, Applicants submit that the present application has provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of the foregoing 35 U.S.C. § 112, first paragraph rejection over claims 43-46 and 48.

CONCLUSIONS

In view of the amendments and remarks made herein, Applicants respectfully submit that the objections and rejections presented by the Examiner are now overcome and that this application is in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

This paper is being filed timely as a request for a three month extension of time is filed concurrently herewith. No additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Applicants submit herewith 1) a request for a three month extension of time; 2) an Associate Power of Attorney; and 3) an Information Disclosure Statement with accompanying references.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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